IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. *To Be Assigned*
HEIDER *et al.*	Art Unit: *To Be Assigned*
Appl. No. To Be Assigned (Continuation of Appl. No. 09/331,254; § 371 Date: December 21, 1999)	Examiner: *To Be Assigned*
Filed: HEREWITH	Atty. Docket: 0652.1910001/EKS/PSC/PAC
For: **Method for Diagnosis and Therapy of Hodgkin's Lymphomas** (As Amended Herein)	

Preliminary Amendment

Commissioner for Patents
Washington, D.C. 20231

Sir:

It is respectfully requested that the following amendments be entered in advance of substantive examination. This amendment is provided in the following format:

(A) A clean version of each replacement paragraph/section/claim along with clear instructions for entry;

(B) Starting on a separate page, appropriate remarks and arguments. 37 C.F.R. § 1.115 and MPEP 714; and

(C) Starting on a separate page, a marked-up version entitled: "Version with markings to show changes made."

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R.

§ 1.136(a), and any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 19-0036.

Amendments

In the Title:

Please substitute the pending Title of the Invention: Method for Diagnosis and Therapy of Hodgkin Lymphomas, with the following Title of the Invention: Method for Diagnosis and Therapy of Hodgkin's Lymphomas.

In the Specification:

Please substitute the following paragraphs/sections for the pending paragraphs/sections.

On page 1, after the title, please insert the following sentence:

This application is a Continuation of Appl. No. 09/331,254; which has a § 371 date of December 21, 1999, said 09/331,254 is a U.S. National Phase of PCT/EP97/07081, filed December 17, 1997 and published as WO98/28625 on July 2, 1998 in German.

Please substitute the paragraph beginning on page 4, line 17, with the following paragraph:

The invention may be carried out with polyclonal or monoclonal antibodies specific to an epitope which is coded by the exon v10. The preparation of antibodies to known

amino acid sequences can be carried out using methods known *per se* (Catty, 1989). For example, a peptide of this sequence may be prepared synthetically and used as an antigen in an immunisation procedure. Another method is to prepare a fusion protein which contains the desired amino acid sequence, by integrating a nucleic acid (which may be prepared synthetically or, for example, by polymerase chain reaction (PCR) from a suitable probe) which codes for this sequence, into an expression vector and expressing the fusion protein in a host organism. The fusion protein, optionally purified, can then be used as an antigen in an immunisation procedure and insert-specific antibodies or, in the case of monoclonal antibodies, hybridomas which express insert-specific antibodies, are selected by suitable methods. Such methods are known in the art. Heider *et al.* (1993, 1996) and Koopman *et al.* (1993) describe the preparation of antibodies against variant epitopes of CD44.

Please substitute the paragraph beginning on page 6, line 4, with the following paragraph:

For diagnostic purposes, antibody molecules may be linked, for example, to radioactive isotopes such as ^{131}I, ^{111}In, ^{99m}Tc or radioactive compounds (Larson *et al.*, 1991; Thomas *et al.*, 1989; Srivastava, 1988), enzymes such as peroxidase or alkaline phosphatase (Catty and Raykundalia, 1989), with fluorescent dyes (Johnson, 1989) or biotin molecules (Guesdon *et al.*, 1979). For therapeutic applications, v10-specific antibody molecules may be linked to radioisotopes such as ^{90}Y, ^{111}In, ^{131}I or ^{186}Re (Quadri *et al.*, 1993; Lenhard *et al.*, 1985, Vriesendorp *et al.*, 1991; Wilbur *et al.*, 1989), toxins (Vitetta *et al.*, 1991; Vitetta and Thorpe, 1991; Kreitman *et al.*, 1993; Theuer *et al.*, 1993), cytostatics (Schrappe *et al.*, 1992), prodrugs (Wang *et al.*, 1992; Senter *et al.*, 1989) or radioactive compounds. The antibody

may also be linked to a cytosine or another immunomodulatory polypeptide, e.g. tumour necrosis factor or interleukin-2.

Please substitute the paragraph beginning on page 7, line 35, with the following paragraph:

Antibody molecules with the specificity according to the invention and optionally linked with a cytotoxic agent may advantageously be used to treat Hodgkin's lymphomas (lymphogranulomatosis). They may be administered systemically or topically, e.g. by intravenous route (as a bolus or continuous infusion), or by intraperitoneal, intramuscular or subcutaneous injection/infusion. Methods of administering conjugated or non-conjugated antibodies, e.g. complete immunoglobulins, fragments, recombinant humanised molecules etc., are known in the art (Mulshine *et al.*, 1991; Larson *et al.*, 1991; Vitetta and Thorpe, 1991; Vitetta *et al.*, 1991; Breitz *et al.*, 1992, 1995; Press *et al.*, 1989; Weiner *et al.*, 1989, Chatal *et al.*, 1989, Sears *et al.*, 1982).

Please substitute the paragraph beginning on page 10, line 9, with the following paragraph:

Fig. 2: CD44v10 expression in HRS cells in various patient groups. It should be noted that patients with a poor clinical progress, i.e. recurrence or bone marrow involvement, exclusively show more than 10% positive HRS cells, whereas patients with no recurrence have less than 10% positive HRS cells. The difference between these two groups is statistically highly significant.

Please substitute the paragraph beginning on page 11, line 5, with the following paragraph:

The entire variant region of the HPKII type of CD44v (Hofmann *et al.*, 1991) was amplified from human keratinocyte cDNA by polymerase chain reaction (PCR). The two PCR primers *5'*-CAGGCTGGGAGCCAAATGAAGAAAATG-*3'* (SEQ ID NO:3), positions 25-52, and *5'*-TGATAAGGAACGATTGACATTAGAGTTGGA-*3'* (SEQ ID NO:4), positions 1013-984 of the LCLC97-variant region as described by Hofmann *et al.* contained an *Eco*RI recognition site which was used to clone the PCR product directly into the vector pGEX-2T (Smith *et al.*, 1988). The resulting construct (pGEX CD44v HPKII, v3-v10) codes for a fusion protein of ~70 kD, consisting of glutathione-S-transferase from *Schistosoma japonicum* and the exons v3-v10 from human CD44 (Heider *et al.*, 1993). The fusion protein was expressed in *E. coli* and then affinity-purified over glutathione-agarose (Smith *et al.*, 1988).

In the Claims:

Please cancel claims 1-16.

Please add the following new claims:

17. (New) A pharmaceutical composition comprising a pharmaceutically acceptable amount of an antibody molecule specific for an epitope within the amino acid

sequence coded by the variable exon v10 of the CD44 gene, wherein the composition comprises a suitable adjuvant or the composition is in freeze-dried form.

18. (New) The pharmaceutical composition of claim 17, wherein the amino acid sequence is SEQ ID NO:2.

19. (New) The pharmaceutical composition of claim 17, wherein the antibody molecule is selected from the group consisting of: a monoclonal antibody, Fab-fragment of an immunoglobulin, a $F(ab')_2$-fragment of an immunoglobulin, and a recombinantly produced antibody.

20. (New) The pharmaceutical composition of claim 19, wherein the recombinantly produced antibody is selected from the group consisting of: a recombinantly produced chimeric antibody, a recombinantly produced humanized antibody and a recombinantly produced single chain antibody (scFv).

21. (New) The pharmaceutical composition of claim 17, wherein the antibody molecule is linked to a radioactive isotope, radioactive compound, enzyme, toxin, cytostatic, prodrug or immunomodulatory polypeptide.

22. (New) The pharmaceutical composition of claim 21, wherein the immunomodulatory polypeptide is a cytokine.

Remarks

Upon entry of the foregoing amendment, claims 17-22 are pending in the application, with claim 17 being the independent claim. Claims 1-16 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. Applicants retain the right to pursue the subject matter of the canceled claims in continuing or divisional applications. New claims 17-22 are sought to be added. Support for the new claims can be throughout the specification and the original claims. Specifically, support for claim 17 can be found, for example, at page 3, lines 22-28; page 4, lines 17-19; and page 8, lines 14-22. Support for claim 18 can be found, for example at page 3, lines 30-35; claims 19 and 20 at page 5, line 4 to page 6, line 2; and claims 21 and 22, at page 4, lines 3-7. These changes are believed to introduce no new matter, and their entry is respectfully requested.

It is believed that the application is now in condition for examination. Early notice to this effect is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

***In the Title*:**

The title has been amended as follows: Method for the Diagnosis and Therapy of Hodgkin's Lymphomas [Method for the Diagnosis and Therapy of Hodgkin Lymphomas]

***In the Specification*:**

On page 1, immediately below the title, the following text has been added:

This application is a Continuation of Appl. No. 09/331,254; which has a § 371 date of December 21, 1999, said 09/331,254 is a U.S. National Phase of PCT/EP97/07081, filed December 17, 1997 and published as WO98/28625 on July 2, 1998 in German.

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fusion protein was expressed in *E. coli* and then affinity-purified over glutathione-agarose (Smith *et al.*, 1988).

***In the Claims*:**

Claims 1-16 have been canceled.

Claims 17-23 have been newly added.